CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES

EDITORIAL: INTRAVENOUS CO-INFUSION OF ADENOSINE AND NOREPINEPHRINE

Robert A. Kloner, MD, PhD*
Gregory Kay, MD**

The birth and increasing popularity of minimally invasive directed coronary artery bypass grafting (CABG) require new ways of better protecting the heart during such procedures since standard cardioplegic techniques are not possible with this approach. There have been anecdotal reports of protecting the myocardium to be revascularized by actually inducing brief coronary artery occlusions followed by reperfusion (ischemic preconditioning). An alternate technique would be to consider "chemical preconditioning" before interrupting blood supply to protect the myocardium.[1] The concept of chemical preconditioning is one in which preconditioning-mimetic drugs, which are known to stimulate the biochemical pathways of preconditioning, but without inducing ischemia, are administered several minutes before coronary artery occlusion. The work of Liu and coworkers[2] has shown that adenosine receptor stimulation is an important mechanism of preconditioning. Both his group and our group have shown that the adenosine receptor agonist R(-)-*N*-(2-phenylisopropyl-adenosine, when administered before coronary occlusion, reduces the size of myocardial infarctions in rabbits.[3] That adenosine may be important for the preconditioning phenomenon in human beings was suggested by recent angioplasty studies. Repetitive coronary occlusion and reperfusion induced by angioplasty balloon inflation and deflation in patients is accompanied by a progressive decrease in chest pain, ST segment deflection, and lactate production. It has been suggested that this observation is a clinical counterpart to preconditioning. Adenosine blockers will prevent the beneficial effects of repetitive balloon inflation; conversely, adenosine administered before angioplasty was shown to reduce initial ST segment change during the first balloon inflation.[4] A brief catecholamine stimulation with an α_1-adrenergic agent several minutes before coronary artery occlusion will also precondition the heart.[5] The problem with administering adenosine or agents such as norepinephrine alone is their profound hemodynamic effects. Cohen and coworkers[6] are to be congratulated on their clever article in this issue of *The Journal of Thoracic and Cardiovascular Surgery.* They have shown that by giving adenosine and norepinephrine together, they counteract much of the adverse hemodynamic effects of either of these drugs alone and still obtain a substantial preconditioning effect. This observation has potentially important clinical implications for the application of such therapy to ischemic syndromes.

For chemical preconditioning to work, the dose of preconditioning-mimetic drugs must be administered temporally close to the long occlusion. Thus Cohen and associates[6] showed that norepinephrine plus adenosine significantly reduced experimental infarct size when given over 5 minutes starting 15 minutes before the long coronary artery occlusion. However, the beneficial effect was less impressive if the pharmacologic agents were given 60 minutes before coronary artery occlusion; and the effect was totally lost when the agents were given 120 minutes before the coronary artery occlusion. A similar time course has been observed when preconditioning was

From The Heart Institute, Good Samaritan Hospital, University of Southern California, Los Angeles, Calif.

Requested for publication March 13, 1997; received April 16, 1997; accepted for publication April 17, 1997.

Address for reprints: Robert A. Kloner, MD, PhD, Heart Institute Research Laboratory, Good Samaritan Hospital, 1225 Wilshire Blvd., Los Angeles, CA 90017.

*Director of Research, The Heart Institute, Good Samaritan Hospital; Professor of Medicine, Section of Cardiology, University of Southern California, Los Angeles, Calif.

**Chief of Thoracic/Cardiovascular Surgery, The Heart Institute, Good Samaritan Hospital, Los Angeles, Calif.

J Thorac Cardiovasc Surg 1997;114:234-5

0022-5223/97 $5.00 + 0 **12/1/82764**

induced not by drugs but by brief periods of ischemia created by coronary artery occlusion.

If chemical preconditioning with adenosine plus norepinephrine before minimally invasive directed CAGB works, it could be extended as an adjunct to cardioplegia in more routine cases of CABG, or possibly these agents could be injected into the vasculature of excised donor hearts destined for transplantation.[7] The premise of chemical preconditioning (and its advantage over mechanical preconditioning) is clear for the cardiac surgery patient: (1) Chemical preconditioning need not interrupt the flow of the operation; (2) the entire myocardium is protected, not just the distribution of the single artery that is temporarily occluded; and (3) there is no trauma to the vessels. While current myocardial protection is excellent, it is not perfect. Stunning is still seen in the clinical setting and results in significant morbidity. At a recent meeting, Mentzer and colleagues[8] suggested that adenosine may be useful as an adjunct to cardioplegia, and one possible mechanism for this is by stimulating the preconditioning pathway. Adenosine pretreatment before cardiopulmonary bypass was associated with better left ventricular function assessed by echocardiography and less use of inotropic agents in the postoperative phase. Again, a major advantage of chemical preconditioning is that the cardioprotective pathways of ischemic preconditioning are stimulated without inducing ischemia or postischemic dysfunction before the long occlusion. Whether chemical preconditioning with combinations of adenosine plus norepinephrine will work in patients undergoing minimally invasive directed CABG remains to be determined. Clearly large multicenter studies are needed to address the issue of whether chemical preconditioning can be used to better preserve ventricular myocardium during such procedures. Such a study should randomize patients to placebo versus adenosine plus norepinephrine about 15 minutes before minimally invasive directed CABG. End points could include perioperative myocardial infarction, peak creatine kinase MB isoenzyme, postoperative heart failure, regional wall motion determined by serial echocardiograms, postoperative arrhythmias, length of stay in the hospital, and mortality. If these studies are positive, certainly it would be worth trying this combination of agents as an adjunct to routine CABG.

In summary, Cohen and colleagues[6] have published an intriguing study showing that by combining two otherwise hemodynamically active agents, it is possible to minimize their hemodynamic effect while still causing a preconditioning-like effect. While the concept of ischemic preconditioning has been around for about 11 years, it is now time to try to apply this phenomenon to the therapy of patients with coronary artery disease.

REFERENCES

1. Kloner RA, Yellon D. Does ischemic preconditioning occur in patients? J Am Coll Cardiol 1994;24:1133-42.
2. Liu GS, Thornton J, Van Winkle DM, et al. Protection against infarction afforded by preconditioning is mediated by A_1, adenosine receptors in rabbit heart. Circulation 1991;84:350-6.
3. Hale SL, Bellows SD, Hammerman H, Kloner RA. An adenosine A_1 receptor, R(-)-*N*-(2-phenylisopropyl-adenosine (PIA) but not adenosine itself, acts as a therapeutic preconditioning-mimetic agent in rabbits. Cardiovasc Res 1993;27: 2140-5.
4. Leesar M, Ahmed M, Broadbent J, Prince C, Stoddard M, Bolli R. Adenosine preconditions human myocardium during PTCA. J Am Coll Cardiol 1996;27(Suppl A):30A.
5. Bankwala Z, Hale SL, Kloner RA. α-Adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines mimics ischemic preconditioning. Circulation 1994;90:1023-8.
6. Cohen MV, Thornton JD, Thornton CS, Sato H, Miki T, Downey JM. Intravenous co-infusion of adenosine and norepinephrine preconditions the heart without adverse hemodynamic effects. J Thorac Cardiovasc Surg 1997;114:236-42.
7. Kloner RA, Przyklenk K, Shook T, Matthews RV, Burstein S, Cannom DS, et al. Clinical aspects of preconditioning and implications for the cardiac surgeon. J Card Surg 1995;10:369-75.
8. Mentzer RM Jr, Canner CC, Chopra PS, Love RB, Rakko PS, Hegge JO, et al. Efficacy of adenosine as an additive to blood cardioplegia in humans during open-heart surgery. Circulation 1995;92(Suppl):I762.